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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/472,232	12/27/99	DUMAS J	BAYER-9-C1

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ART UNIT	**PAPER NUMBER**
1624	10

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/472,232	Dumas et al.
Examiner	**Art Unit**
Deepak Rao	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 7, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *11-14* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10 and 15-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1-25 are pending in this application.

Election/Restriction

Applicant's affirmation of the election with traverse of Group I, claims 1-10 and 15-25 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the restriction is improper because there is no burdensome search involved. This is not found persuasive because the compounds of groups I -III are drawn to structurally dissimilar compounds which are not art recognized equivalents. They are structurally dissimilar such that a reference anticipating a compound may not render the remaining compounds obvious. 37 CFR 1.141(a) provides that two or more independent and distinct inventions may not be claimed in one application, whether or not the misjoinder occurred in one claim or more than one claim. Restriction is going to be exercised where independent and distinct inventions are presented in one Markush grouping. Independent means when the compound is being made and/or used alone, not in combination with other compounds of the Markush expression. Restriction is considered proper in Markush claims where the members are so diverse and unrelated that a prior art reference anticipating the claim with respect to one of the members, would not render the claims obvious under 35 U.S.C. 103 with respect to the other members. Therefore, what should be considered for patentable distinctness is the compound as a whole. Each of the groups are classified separately and further,

the compounds of Groups I-III require separate searches in the literature and therefore, it is burdensome for the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective for the reasons provided in the previous office action. Further, the S.No. of the Provisional Application provided in the declaration (60/135,502) is inconsistent with the first paragraph of the specification. It is acknowledged that applicant will submit a new oath with appropriate corrections in due course.

The following rejections are withdrawn:

The rejections under 35 U.S.C. 112, second paragraph of the previous office action are withdrawn in view of applicant's amendments, except one which is maintained in this office action.

The following rejections are maintained:

1. Claims 15-23 are rejected under 35 U.S.C. 112, first paragraph for the reasons provided in the previous office action which are incorporated herein by reference. Applicant's arguments are fully considered. Applicant relies on a recent board decision *Ex parte Henning* (S.No. 08/628,250), however, this decision is not a published decision and therefore, can not be obtained in the USPQ. Further, at the present time, the above referred application is unavailable to the examiner and could not be reviewed. Applicant argues that the compounds 'treat cancers that are mediated by raf kinase'. However, the claim recites "the treatment of a disease mediated by raf kinase" which includes diseases other than cancers and the specification only provides enabling disclosure with regards to cancer and based on the *in vitro* and *in vivo* test procedures provided. Further, there is insufficient guidance or direction provided regarding how this treatment is practiced. The claim does not identify a subject or host that is the recipient of the treatment.

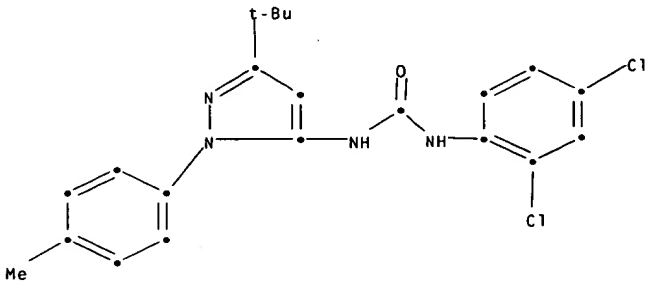
2. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation "effective to inhibit raf" appears to be incomplete. The specification discloses that the enzyme is 'raf kinase' and therefore, the enzyme should be referred as disclosed. Applicant neither amended the claim nor provided any explanation regarding this issue.

3. Claims 1-10 and 24-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Regan et al., U.S. Patent No. 6,080,763 (filed October 29, 1998 and having an effective filing date of

November 3, 1997). Applicant's arguments are fully considered but they were not deemed to be persuasive. Applicant argues that 'the disclosure relied on in making the rejection is not prior art'. First, as per the updated continuing data, the instant application is a continuation of S.No. 09/303,621 (filed December 22, 1998) which claims the benefit of Provisional Application No. 60/126,439 (filed December 22, 1997). The Provisional Application on which applicant is relying on for the priority benefit, does not disclose the instantly claimed pyrazolyl compounds. Accordingly, applicant is not entitled for the priority date of December 22, 1997. Therefore, US'763 which was filed October 29, 1998 is available as prior art for the instant claims. Next, contrary to applicant's argument, the priority document of US'763 (i.e., Provisional Application No. 60/064,102) clearly discloses the compounds relied upon for the rejection under 102(e). The provisional application disclosed generic formula (I) on page 4 and exemplary compounds on page 9, see e.g., at line 11 the reference discloses the compound **N-(3-t-butyl-1-(4-methylpheny)pyrazol-5-yl)-N'-(2,4-dichlorophenyl)urea,** which is embraced by the instantly claimed genus. Therefore, in view of the above, the rejection under 35 U.S.C. 102(e) is maintained.

4. Claims 1-10 and 24-25 are rejected under 35 U.S.C. 103(a) as obvious over Regan et al., U.S. Patent No. 6,080,763, for the reasons of the previous office action which are incorporated herein by reference. Applicant's arguments are fully considered but they were not deemed to be persuasive. Applicant argues that the reference teaches a large genus without teaching any compounds that have the same 2,5-substituent pattern of the ureas claimed in the instant

application. However, as explained above, the reference clearly teaches a generic group of compounds (see formula (I) in page 4 of the Provisional Application 60/064,102) and further discloses several compounds (see page 9) including "N-(3-t-butyl-1-(4-methylpheny)pyrazol-5-yl)-N'-(2,4-dichlorophenyl)urea" (see line 11), which is structurally depicted below:



This compound fits in the instantly claimed structural formula of A-NH-C(=O)-NH-B wherein A is a pyrazolyl; R^1 is C_4 alkyl; R^2 is 4-methylphenyl; and B is 2,4-dichlorophenyl. Applicant cites *In re Baird* and argue that the genus of the reference is not sufficient to establish a *prima facie* case of obviousness. This is not found to be persuasive because the decision in *Baird* was based on a big genus encompassing millions of compounds vs. a small number of claimed species, "[A] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds." 29 USPQ2d 1552. However, the instant case involves a genus vs. subgenus, more specifically, the reference clearly teaches a generic group of compounds that embraces the instantly claimed genus and further discloses a specific species that falls within the instantly claimed genus and thus, the instantly claimed compounds are clearly suggested by the reference.

Therefore, In re Baird is not on point. For all the above reasons, the rejection under 35 U.S.C. 103(a) is maintained.

5. Claims 1-5, 7-10 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Creswell et al., U.S. Patent No. 5,162,360 for the reasons provided in the previous office action which are incorporated herein by reference. Applicant's arguments are fully considered but they were not deemed to be persuasive. Applicant argues that the 'broad generic disclosure provides no guidance to prepare the compounds' instantly claimed. However, the reference clearly teaches urea derivatives of formula I wherein Het is a pyrazolyl of formula (8) wherein R_{10} is C_{1-16} alkyl and further, discloses a specific compound having a C_{12} alkyl substituent on the pyrazolyl. Furthermore, the reference discloses other compounds having pentyl (C_5), hexyl (C_6), decyl (C_{10}), etc. for the alkyl substituent. Therefore, the reference clearly teaches compounds having various sizes of alkyl substituents and thus provides motivation to one skilled in the art to prepare the compounds within the genus by varying the size of the alkyl substituent. Such modification would have been obvious to one of ordinary skill in the art in the absence of unexpected results.

The following rejections are under new grounds:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-10, 17-20 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First, in the claims the variable Ar is defined to be "5-10 membered aromatic structure", see for example, claim 1, page 3 of paper no.9, line 4. This recitation is not fully supported by the description in the specification because the specification defines Ar to be "5- or 6-member aromatic structure", see page 4, line 12. The specification does not describe an aromatic structure having more than six members and thus, there is no support for the instant recitation of "5-10 member aromatic structure" which includes aromatic structures having '7-10 members' also.

Second, in claim 4, B is defined as a group $-Q(X_{n-1})-(Y-Q^1-Z_{n1})_s$ (see page 5, line 2) which group is different from original claim 4 and the original disclosure, see page 6 of the specification. The group Z_{n1} is enclosed within the parenthesis, which is understood to indicate that Z_{n1} is a substituent on Q^1. However, the subscript of X is changed to "n-1" for which there is no adequate support in the disclosure. This subscript is confusing and unclear which issues are addressed in a rejection under 112, second paragraph.

The generic disclosure nor the examples provide any support for the above mentioned subject matter. Therefore, it is concluded that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2. Claims 1-10 and 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein B is as disclosed in the examples, does not reasonably provide enablement for all other compounds generically embraced by the definition provided for B. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification fails to enable the preparation of the claimed compounds. From the schemes in the specification, it is clear that the corresponding amines of A and B are the essential starting materials to prepare the claimed compounds, see pages 10-13. However, there is no disclosure regarding how these starting materials, particularly pertaining to B are obtained. The instant claim 4 defines B to be a specific group (see line 2), wherein the definition of Q^1 includes a 3-member aromatic ring structure and the specification does not provide any disclosure regarding the starting materials required to prepare such compounds. All the examples are drawn to compounds wherein B is phenyl or substituted phenyl, which are structurally different from those embraced by the definition provided for B. In view of the lack of direction provided in the

specification regarding starting materials, the lack of working examples commensurate in scope with the claims and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore, practice the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims in the definition of B (all occurrences), the term "containing" (see for example, claim 1, page 2, line 6) is open ended. 'Containing' leaves the claim open for the inclusion of unspecified groups and/or substituents. The use of the above phrase causes the claim to be broader than the invention. See *In re Fenton*, 451 F.2d 640, 171 USPQ 693 (CCPA 1971).

2. In claim 3, B is defined as tricyclic moeity having a substituent R^5, see the formulae at line 5. There is insufficient antecedent basis for this limitation in claim 1 on which the claim is dependent. According to claim 1, B can be substituted upto 'n' times by a group X which is further defined as many groups some of which contain R^5. Therefore, as per claim 1, R^5 does not exist on B when there is no X substituent. Further, the definition of

R^5 is broader than the definition of X, i.e., R^5 definition includes "up to per-halosubstitued C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl" which is not part of the definition provided for X. In claim 1, X definition does not include substituted aryl or heteroaryl groups. (Claim 17 also contains the same discrepancy).

3. In claim 4, the definition of B is unclear. The term X contains a subscript n-1 wherein n is 0-3, therefore, it is unclear what type of substituent is present when n is 0, i.e., X_{-1}. (Claim 18 also contains the same discrepancy).

4. In claim 4, Q^1 is defined as "a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms..." which is confusing and unclear. It is not clear what aromatic rings have 3, 4, 5, etc. carbons. The examples provided show 6 membered aromatic rings. Further, the group Q^1 in claim 4 is equivalent of the group Ar in claim 1. However, the definition of Q^1 is broader than that of Ar, which is confusing. (Claim 18 also contains the same discrepancy).

5. Claim 5 recites the limitation "Y-Q^1 is phthalimidinyl" in line 6. There is insufficient antecedent basis for this limitation in claim 1 on which claim 5 depends from via claim 4. Neither of claims 1 and 4 recite such group. (Claim 19 contains the same discrepancy).

6. Claim 15 recites "a method for the treatment of disease....", however, it does not recite where the disease exists. There is no recitation of relating to 'a subject that is need of such treatment', it is not clear how one identifies the disease without having a patient

suffering from the disease. Further, it is not clear how the administration step is carried out without having a host that is in need of such treatment.

Claim Rejections - 35 U.S.C. § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regan et al., U.S. Patent No. 6,080,763 in view of Bruder et al. (J. Vir. 1997). The primary reference Regan et al. (US'763) teaches a generic group of compounds of formula (I) (see col. 6) and further specific pyrazolyl compounds (see the examples). The reference teaches that these compounds are useful in the treatment of diseases and pathological conditions caused by the release of inflammatory cytokines such as interleukins and tumor necrosis factor from cells, see the development of art in col. 1-5. The primary does not specifically teach that the compounds are useful in the treatment of diseases mediated by raf kinase. Bruder et al., teaches that raf kinase contributes to the production of interleukin which initiates the release of inflammatory cytokines, see page 398, col. 2. One of ordinary skill in the art would have been motivated to use the therapeutic agents of the primary reference for the treatment of disease mediated by raf protein in view of the teachings of the secondary reference. Such modification would have been obvious because the secondary reference teaches that raf kinase triggers the release of inflammatory

cytokines and the skilled artisan would have expected to treat inflammatory diseases by inhibiting the raf kinase.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
October 18, 2001